Age-specific reference ranges for serum prostate specific antigen in South Indian men

Dissertation submitted in partial fulfillment of the requirements for the degree of

M.Ch (Genitourinary Surgery)

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CERTIFICATE

This is to certify that the dissertation entitled **Age-specific reference ranges for serum prostate specific antigen in South Indian men** done under our supervision and is the bonafide work of **Dr.K.V.Arasi**. It is submitted in partial fulfillment of the requirement for the M.Ch. (Genitourinary surgery) examination.

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CONTENTS

INTRODUCTION

Prostate-specific antigen (PSA) is the most clinically useful tumour marker available today for the diagnosis and management of prostate cancer; unlike other tumor markers prostate specific antigen is not cancer specific. Overlapping serum PSA concentrations between benign prostatic hyperplasia and prostatic adenocarcinoma limit the effectiveness of serum PSA in detecting early prostate cancer.

Several concepts have been devised to optimize the diagnostic value of serum PSA. Various PSA relation markers have been advocated for the differentiation between benign prostate hypertrophy and carcinoma in so called "gray zone" level of total PSA.

Age specific PSA reference ranges provide greater sensitivity for cancer detection in younger men at the expense of a greater negative biopsy rate. In older men unnecessary biopsies could be spared.

Studies [32,35,42,44] have reported varying concentrations of PSA in serum of healthy males belonging to different races. There are very few Indian studies only. Hence we deliberately felt it was essential to establish our own age specific reference ranges.

AIM

To determine age-specific reference ranges for serum prostate-specific antigen (PSA) concentration in South Indian men.

REVIEW OF LITERATURE

PSA is a serine protease secreted exclusively by the epithelial cells of the prostate and also in minute quantities by the epithelial lining of periurethral glands. Its major physiological role is to promote the liquefaction of seminal clot. It is androgen regulated and one of the most abundant serine protease in the seminal plasma (1,000,000 ng/ml)

History [24]

In 1970, Ablin R.J. et al.[2] identified two separate prostatic tissue-specific antigens. One of the antigens was identified, as prostatic acid phosphatase, while the other, the forerunner of the current PSA remained unnamed. In 1971, Hara et al. identified a protein in seminal fluid. They called it gamma-seminoprotein.

A few years later (1979) Wang, Chu et al. purified the antigen from prostatic tissue and named it prostate-specific antigen.

Papsidero and associates detected PSA in human serum in 1980. These researchers were the first to demonstrate the relationship of PSA to prostate cancer.

Because PSA is produced by the body and can be used to detect disease, it is sometimes called a biological marker or tumor marker. Prostatic intraepithelial neoplasia does not cause disruption of the basement membrane and does not raise serum PSA.

PSA paradox [37]

Normal prostate epithelial cells and benign hyperplastic tissue produce more PSA than malignant prostatic tissue. In localized and metastatic prostate cancer the expression of PSA per cell is reduced, but there is an increase in the level of serum PSA. Malignancy is typically associated with a lower degree of differentiation; therefore the relative number of terminally differentiated cells will decline, as well as the expression of differentiation markers such as serum PSA. Malignancy results in loss of polarity and basal cell numbers and disruption of basement membrane, leakage of PSA to circulation.

In prostate cancer, serum PSA is determined by the number of cancer cells and the expression of PSA per cancer cell. Considering the more aggressive cancer cells produce less PSA, the phenomena counteract one another. This explains why PSA is a poor marker in cancer progression

Nonprostatic sources of PSA

The name PSA reflects the initial widespread belief that expression of the protein was restricted to the prostate gland. However this notion has been dispelled. Numerous studies have shown that PSA is expressed extraprostatically. Low levels of PSA^{3} have been detected in various tissues that express steroid receptor super family, including uterine endometrium, breast tissue, peri anal & peri uretheral glands, salivary glands, adrenal and renal neoplasm's and various other malignant tumours. In 1993 Iwakini et al[54]. showed PSA secretion from periurethral glands by immunohistochemical studies. Oesterling[8] et al suggested that the periurethral glands do not have a clinically significant effect on serum PSA concentration after radical prostatectomy.

Growth and Development of Human Prostate[9]:

Human prostate undergoes an increase in size and develops histological evidence of stimulated growth during three periods of life[9]. Before and at birth, during puberty, with advancement of age. The average weight of prostate is as follows

1 to 10 years – 1.4 g,
11 to 20 years - 10.8 g,
21 to 30 years - 18.g,
41 to 50 years - 20.2g.
In 6th decade 30.9
8th decade to 38.8 g

The prostate-specific antigen (PSA) test

Gutman and Gutman in 1938, described acid phosphates as a tumour marker for prostatic cancer. Acid phosphatase was replaced by serum PSA because of its low sensitivity and specificity. A PSA test measures the amount of prostate-specific antigen in the blood. Low amounts of PSA may be found in the blood of healthy men. The amount of PSA in the blood normally increases as a man's prostate enlarges with age. It is also

increased by inflammation of the prostate gland, prostate cancer, manipulation, and urinary retention

Prostate-specific antigen test is done to determine whether lumps found during a digital rectal exam or a transrectal ultrasound may be caused by prostate cancer, to monitor the development of prostate cancer and the response to treatment. If PSA levels are increasing, the cancer may be growing or spreading. Successful treatment of prostate cancer usually causes PSA levels to drop. The amount of PSA is often undetectable in a man who has been treated for prostate cancer by having his prostate gland removed. PSA levels that rise after prostate removal indicate that the cancer may have spread to another part of the body or has recurred at the prostate site.

Commercial Assays:

Commercial PSA assays measure the glycoprotein in the serum using immuno- assays. It is important that the assay be performed in the same laboratory for comparative purposes over time. Some assays are immunoradiometric and some are enzyme-immunoassays the importance of the PSA test in early detection

is based on establishing a baseline value and doing the PSAs over time on a regular interval, usually one year.

Assay kits for total PSA

Table - 1

Assay kit	Capture antibody	Tracer antibody	Minimal detectable limit (micro gram/L)
Bayer ADVIA centaur	m	Sh (Sheep poly clonal)	0.06
Can Ag ELISA	m	m	0.10
CIS ELSA-2	m	m (monoclonal)	0.14

Advice to the patient

1. Refrain from sexual activity for 2 to 3 days prior to testing.
2. To wait for one week after having a cystoscopy[29]. (Baseline level reached in 3 days)
3. To wait until a urinary tract infection or prostatitis has cleared up.
4. To wait for 6 weeks[29] after a needle biopsy or TUR before doing PSA test

Inaccurate test results:

1. Recent sexual activity or a cystoscopy test may cause prostate-specific antigen (PSA) levels to rise. Osterling and colleagues[57] prospectively randomized 69 men into 3 group's flexible cystoscopy, rigid cystoscopy and control. Two serum PSA levels were estimated. They found the median serum PSA after flexible cystoscopy was 0.1ng/ml, rigid cystoscopy and control was 0.05ng/ml.
2. Large doses of some medications used to treat cancer—such as cyclophosphamide diethylstilbestrol, and methotrexate - can interfere with test results.
3. The medication finasteride, used to prevent further enlargement of the prostate gland in men with benign prostatic hypertrophy (BPH), can cause inaccurately low PSA levels. Finastride[24] decreases total PSA and PSA density; free PSA is not affected.
4. Herbal supplements can also affect PSA levels.
5. Contamination or inadequate refrigeration of the blood sample can cause inaccurate test results.

DEFINITIONS.

Sensitivity: Is the capability of a test to identify the presence of disease expressed as the ratio of true positives to the sum of true positives and false negatives. . PSA has a sensitivity of 80%.

Specificity: Is the capability of a test to identify the absence of disease expressed as the ratio of true negatives to the sum of true negatives and false positives. PSA has a specificity of 35-50%.

Positive predictive value: Is the capability of a test to identify patients with disease among all patients demonstrating positive results.

False positive test:

False positive test results occur when the PSA level is elevated but no cancer is actually present. False positives may lead to additional medical procedures that have potential risks and significant financial costs and can create anxiety for the patient and his family. Most men with an elevated PSA test turn out not to have cancer. Only 25 to 30 percent of men who have a

biopsy due to elevated PSA levels actually have prostate cancer. In general 5-8 percent of a screening population will have an abnormal DRE. A value between 4-10 ng/ml has a 15-30% chance of being positive. Values above 10 are associated with a positive biopsy in greater than two thirds of cases upper limit of normal for PSA is controversial. Recent studies[23]suggest that using a PSA cutoff of 2.5 ng/ml for men younger than 60 years may be more appropriate.

False negative tests: False negative test results occur when the PSA level is in the normal range even though prostate cancer is actually present. Most prostate cancers are slow growing and may exist for decades before they are large enough to cause symptoms. Subsequent PSA tests may indicate a problem before the disease progresses significantly. Cancers missed by the age specific reference ranges in older men (>69 years) were predominantly small, organ confined, unlikely to be life-threatening [25] and avoids invasive prostatic biopsies.

Strategies for enhancing Prostate specific antigen specificity;

Attempts to improve the specificity of serum PSA determinations as a risk indicator for prostate cancer have focused on the following approaches;

1. Age specific PSA
2. PSA density
3. PSA velocity
4. PSA transition zone density
5. Free to total PSA ratio
6. ACT alpha 1 complex PSA

Age specific reference ranges.

PSA is also age dependent, studies[25] have shown that age was found to contribute independently of volume to serum PSA, accounting for 5% of variance in serum PSA concentration. PSAD correlates directly with age. Factors intrinsic to the aging prostate play a role in the variation serum PSA with advancing age. Osterling et al[55], showed the clinical usefulness of age specific PSA by noting an increase in specificity by 11% and positive predictive value by 5%.

Osterling et al[56], have concluded that when age specific reference ranges were used PSAD does not contribute additional information. Data has shown 96% agreement between PSA and PSAD.

Age specific reference range sensitivity:

Studies have shown that age specific reference ranges decrease the sensitivity of PSA in older men (>6o years) but improve it younger men.

Criley SR et al[26] has reported that age specific reference ranges increase the potential for detection of prostate cancer by 18% in men 50 years old or younger and decreased detection by 19% in men 69 years old or older. The following is a guideline adjusted for age[3].

Age 40-49	0.0-2.5 ng/ml
Age 50-59	0.0-3.5 ng/ml
Age 60-69	0.0-4.5 ng/ml
Age 70-79	0.0-6.5 ng/ml

Age specific reference range according to individual year of life [25]. (Table -2)

Table – 2

Age Years	PSA range ngs/ml	Age Years	PSA range ng/ml
40	2.0	60	3.8
41	2.1	61	4.0
42	2.2	62	4.1
43	2.3	63	4.2
44	2.3	64	4.4
45	2.4	65	4.5
46	2.5	66	4.6
47	2.6	67	4.7
48	2.6	68	4.9
49	2.7	69	5.1
50	2.8	70	5.3
51	2.9	71	5.4
52	3.0	72	5.6
53	3.1	73	5.8
54	3.2	74	6.0
55	3.3	75	6.2
56	3.4	76	6.4
57	3.5	77	6.6
58	3.6	78	6.8
59	3.7	79	7.0

Algorithm for the use of age specific reference ranges: [25] (Table – 3)

Table – 3[(25)]

PSA	DRE	DIAGNOSTIC ACTION
Less than or equal to age specific range	Negative	Annual PSA, DRE
Greater than age specific range	Negative	TRUS; biopsy visible lesions, systemic sextant biopsy, with two cores containing transition zone
Any value	Positive	TRUS; biopsy palpable and visible lesions, sextant biopsy of remaining prostate

The normal 4.0 ng/ml is no longer recognized as the cutoff point. A recent study has reported that 15% of men with a normal DRE and a PSA level of < 4ng /ml have cancer detected on systemic needle biopsies. The current American cancer society and the 2004 National Comprehensive Cancer Center Network guidelines also recommend considering a biopsy for a PSA level of > 2.5 ng / ml [23].

It is important to recognize that the real value of the PSA test in early detection is based on establishing a baseline PSA value and regularly, on a yearly basis, measuring the PSA to observe changes from the baseline value. Incremental changes of 0.75 ng/ml in a year should be investigated.

Catolona WJ et al [23] said that a trend is more important than any single PSA value and one must always remember that PSA is not specific for cancer.

Age adjusted PSA.

Concept of raising PSA threshold in older patients and lowering it in younger patients. Data suggests normal PSA of 2.5 may be more appropriate in men under the age of 60. Many suggest lowering value for young men and maintaining 4.0 for older patients to minimize "miss rate" in this population

PSA density

Benson et al[49] introduced the term PSA density to correct PSA for prostatic volume. PSA density is the value of the PSA divided by the size of the prostate. The likelihood of prostate cancer is increased when the PSAD value is high.

Prostate biopsy is recommended in men with normal DRE, PSA between 4 to 10 ng /ml and PSAD of 0.15 or greater The use of PSA density [13] to interpret PSA results is controversial because cancer might be overlooked in a man with an enlarged prostate.

Recent large studies conducted by Brawer and associates[47] have not confirmed the utility of PSA density. Catalona and associates[48] documented that approximately 50 % of CaP would have been missed using a cut off of 0.15, this may be due to difficulty in obtaining reproducible prostatic volume by TRUS.

PSA transition zone density[38]

Transition zone adjusted PSA were used in an attempt improve the specificity of prostate cancer. Calculated threshold for transition zone PSA density of 0.35 ng/ml provided the highest positive predictive value for prostate cancer detection in patients with tPSA <10 ng /ml. Because of the greater variability in the determination of PV the use of transition zone PSA density remained as an investigational tool for early detection of prostate cancer.

PSA velocity:

PSA velocity is based on changes in PSA levels over time. Carter and colleagues[50] in a long term prospective study found the average rate of change of serum PSA over three consecutive PSA determinations had a better specificity (90 %) for detecting prostatic cancer as compared to 60 % when PSA greater than 4 ng/ml was the detection criteria. A sharp rise in the PSA level raises the suspicion of cancer. PSA levels appear to increase more slowly in men with prostate enlargement.

The rate of changes in the PSA[50] more than 0.75 ng/ml per year was a specific marker for cancer. PSA velocity cut offs have not been determined for men with PSA values less than 4 ng/ml. Less 5% of men with out a history of prostate cancer have PSA velocity of more than 0.75 ng/ml/y.

Carter et al[21], suggested a minimum length of follow up of 18 months is needed to use PSA velocity for cancer detection. The test is used as a tool to keep track of how PSA levels change, but it is not used to diagnose prostate cancer.

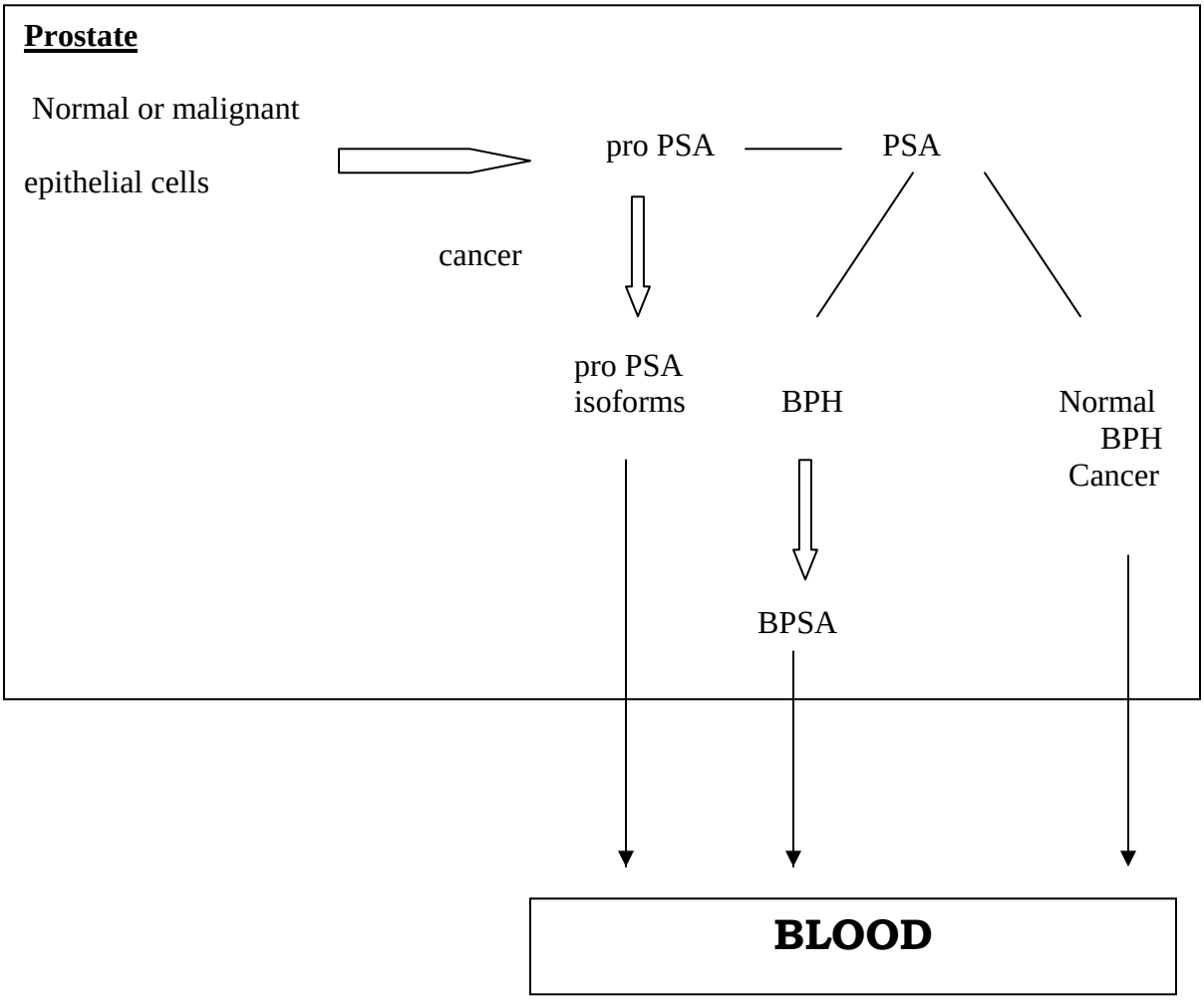
If PSA increases dramatically in a short period, it may be one indicator that prostate cancer has progressed.

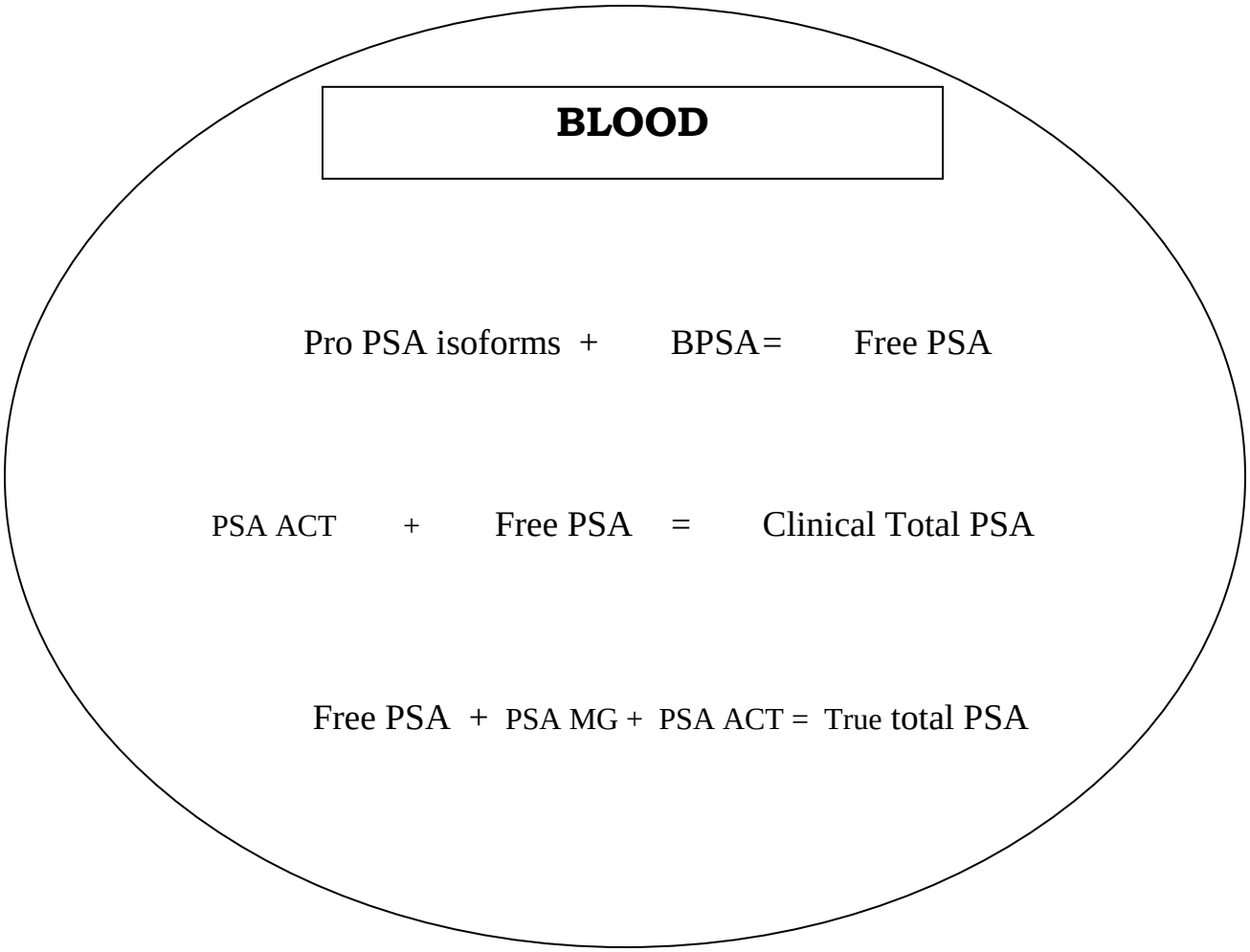
Recent study by D'Amico et al[5] published in the New England Journal of Medicine suggested that an annual PSA velocity of 2 ng/ml or greater was independently associated with prostate cancer mortality after radical prostatectomy. Potentially this may serve as a marker for identifying patients who may be considered for novel neoadjuvant strategies before undergoing surgery.

Molecular forms of PSA

In 1990, Christensson et al. discovered that PSA exists in more than one form circulating in serum. These forms are: Free PSA (PSA-f), bound PSA (PSA-ACT) and complexed PSA (PSA-MG). Most of the PSA in the sera is bound to the antiproteases ACT and MG Binding of PSA to ACT inactivates the protease, but it is immunodetectable. Since the complexed form, PSA-MG is not immunoreactive[4]; it is not measured by any of the available commercial assays at the present time. Total PSA is a combination of PSA-f (10- 30 %) and PSA-ACT (65 –90%).

Mechanism of formation of different forms of PSA





Free PSA:

Free PSA in serum[37] is composed of three distinct forms: pro PSA, BPSA, and intact PSA that may have structural or conformational changes that makes it inactive. All forms of free PSA are enzymatically inactive BPSA, is a degraded form of PSA that has been shown to be associated with prostate BPH transition zone tissue.

Free PSA (BPSA) concentration is more in benign prostatic hyperplasia, while cancer produces more of the attached form. This difference may be due to differential expression of PSA isoforms by transition zone compared with peripheral zone. Cancer produces more of pro PSA.

In the intermediate PSA range between 4 to 10 ng /ml the percentage of free PSA[19] provided important information regarding the presence of cancer. If percent free PSA is >25% the probability of a positive biopsy drops from 15-30 percent to 5-7%. Percentage of free PSA cut off 25% detected 95% of cancers while avoiding 20% unnecessary biopsies .Low free PSA values (less than 15%) are more likely to be caused by prostate cancer than high free PSA values.

Percent free PSA[20] and Probability of cancer

Free PSA	Probability of Cancer
Greater than 25%	8%
20 – 25%	16%
15 – 20%	20%
10 – 15%	28%
0 – 10%	56%

The use of f/t PSA has been extensively evaluated and found to greatly improve the specificity of prostate cancer detection. At 85 % and 95%sensitivity free PSA provided the highest Specificity.

Precursor PSA (pPSA).

Molecular form of free PSA. PSA is secreted from the prostate luminal epithelial cells as pPSA, an inactive proenzyme containing a 7-amino acid pro-leader peptide and 237 amino acids of mature PSA. The pro-leader peptide is removed extracellularly to produce active, mature PSA. Since no pPSA forms have been found in seminal plasma, pPSA has been

identified as a serum marker with greater cancer specificity[6]. Precursor –PSA[27] has shown some early results in detecting prostate cancer at PSA levels of 2 –10 ng/ml

Complexed prostate-specific antigen (cPSA) is a fairly new test to help detect prostate cancer. Ozdal et al[38] have suggested that complexed PSA is similar to the total PSA in sensitivity but complex PSA is more specific than t PSA. Complex PSA alone has lower validity than the ratio of free and total PSA. At a sensitivity of 90% the cPSA /PV ratio with a threshold of 0.08 provided the highest specificity. However, at a sensitivity of 95 % f/tPSA provided the highest specificity[38]. The cPSA test currently is not widely available. As a single test for screening, cPSA may improve specificity over total PSA and comparable specificity to free-to-total PSA for prostate cancer detection, and may reduce the number of unnecessary prostate biopsies in the 2.6-4.0-ng/mL - tPSA range[7].

Molecular forms of PSA and age;

Following a community based study; Oesterling et al[46] concluded that the individual serum concentrations of free PSA, total PSA and complexed PSA all correlated with the patient's age. The ratios of free to total PSA, complexed to total PSA, free to complexed PSA were constant for men of all ages. Complexed and total PSA all correlated directly with the patient's age.

Risk factor for carcinoma prostate

Ries LAG et al[58], has shown that age is the most common risk factor, with nearly 70 percent of prostate cancer cases occurring in men age 65 years and older .The post pubertal presence of an intact hypothalamo pituitary testicular axis is required for the development of carcinoma prostate. Men castrated before onset of puberty have little risk of developing carcinoma prostate**.**

Other risk factors for prostate cancer include family history, race[30], and possibly diet. Men who have a father or brother with prostate cancer have a greater chance of developing prostate cancer.

Eldon et al[39] found that female relatives are not at higher risk of breast cancer but they may be at greater risk of kidney cancer. African American men have the highest rate of prostate cancer[40], while Asian and Native American men have the lowest rates. In addition, there is some evidence that a diet higher in fat, especially animal fat, may increase the risk of prostate cancer.

Prostate cancer screening:

Using the PSA test to screen men for prostate cancer is controversial[31] because it is not yet known if this test actually saves lives. Moreover, it is not clear if the benefits of PSA screening outweigh the risks of follow-up diagnostic tests and cancer treatments. The PSA test may detect small cancers that would never become life threatening. This situation, called over diagnosis, puts men at risk for complications from unnecessary treatment. Despite these controversies PSA monitoring fulfills the prerequisites of a screening programme. The estimated increase in detection lead time[10] is approximately 5 years.

The American Cancer Society, American Radiological Association, and American Urological Association recommends

early detection with an annual DRE and PSA beginning at age 50 for all men with a life expectancy greater than 10 years and age 40 for men of African American race[30] or a family history of prostate cancer.

The 2004 recommendation of a consensus panel from the National Comprehensive Cancer Network recommends a baseline PSA at age 40 for all men. Those men with a serum PSA equal or greater to 0.6 ng/ml (the median PSA for that age group) should undergo yearly screening, whereas those with a value less than 0.6 ng/ml may have another interval PSA at age 45. The same rule applies at age 45

Catalona WJ et al[23], recommends:

1. Annual PSA testing and a DRE at 40 years
2. Earlier screening for men with family history
3. Prospectively monitoring PSA velocity
4. Biopsies for men with a suspicious DRE, PSA>2.5 ng/ml
5. Using free PSA, cPSA, PSA density and velocity to determine the need for repeat biopsies.

Recommended frequency of prostate specific antigen measurement[24].

1. Annual PSA for men with normal DRE and a stable PSA of less than 4 ng/ml and greater than 2.5 ng/ml
2. Biannual Screening For Men With a normal DRE and a serum PSA of less than 2.5 ng/ml

No further screening for PSA level of 1 or less in men aged 65 years. (Baltimore longitudinal study, needs additional observations)

Transrectal Ultrasound (TRUS)

TRUS[18] is not recommended as a first line-screening test because of its low predictive value for early prostate cancer. The Transrectal Ultrasound (TRUS) guided biopsies are clearly indicated in men with life expectancy greater than 10 years with abnormal DRE with or with out an elevated PSA. (TRUS) guided biopsies are advised in men with a normal DRE and an elevated PSA.level. Milford ward et al[29] had shown that DRE or TRUS does not cause statistically significant increase in PSA.

Newer tests:

RT- PCR assay

PCA3 formerly called DD3 is the prostate specific gene[28] described to date. Using RT-PCR assay, prostate tumors showed a 66-fold up regulation of DD3 when compared with normal prostatic tissue. This up regulation was found in >95% of prostatic cancer specimen studied. This PCA3 based RT-PCR assay was used to identify prostate cancer in urine sediments obtained after prostatic massage, sensitivity was found to be 67% negative predictive value was 90%. This newer study at this stage appears to improve the accuracy of diagnosis and avoid unnecessary biopsies. Further results are awaited.

Kallikrein tumor markers

The humen kallikrien gene family encodes three known and related proteins:tissue kallilerin ,glandular kallikerin and PSA. There is 78% aminoacid homology between hK2 and PSA. Both Hk2 and PSA are expressed in prostatic epithelium. They are released in a precursor zymogen form and are under androgen regulation. They are present in serum and seminal fluid, and can form complexes with endogenous protease inhibitors.

Human kallikerin 2 like PSA is found almost exclusively with in the prostate. The expression with in the prostate is lower than that of PSA. Black et al[51] has found the PSA and hK 2 ratios in male sera to be 0.1 to 34 and the ratio in seminal plasma are 100 to 500.

Takayama et al[52] believed that human kallikerin 2 plays a role in regulating PSA activity. It cleaves the precursor form of PSA. The expression of hK2 is higher in more poorly differentiated carcinomas than in normal and benign tissues. Preliminary evidence suggests that the ratio of hk2 to PSA may improve the ability of PSA to identify men with prostate cancer. Human glandular kallikrein 2, which belong to the human kallikrein family as well as PSA, is expected as a tumor specific marker.

MATERIALS AND METHODS

Study design

Cross sectional study

Setting

This study analyzed the PSA value of 117 subjects with out lower urinary tract symptoms during the period October 2003 to September 2005 at Government General Hospital. Chennai -3

Inclusion criteria

1. Individuals attending Urology Clinics for minor illness
2. Normal healthy volunteers

Exclusion criteria

1. Subjects with history of lower urinary tract symptoms
2. Subjects with history of recent urethral instrumentation
3. Subjects with history of recent catheterization
4. Patients with history of Prostatitis

Data collection

Our study group consisted of 117subjects belonging to the subpopulation of chennai from south India of different age groups ranging from 40 to 69 years. Detailed history was taken

and a complete clinical examination was done. Blood biochemical analysis and urine analysis were done for all patients. Ultrasound KUBU, digital rectal examination was done in all selected subjects. Complete questionnaire is shown in appendix 1

Serum PSA was estimated[29] using ELISA, and Bayer ADVIA centaur assay kits (last 25 patients).

Case definitions

Subjects referred to Urology department for evaluation of renal cyst, back pain, renal microlith, infertility were included in the study. Three patients with renal calculi with out urinary tract infection were also included in the study. Healthy volunteers (hospital workers, patient's attenders) after through examination and history taking were also included in the study group.

Statistical analysis

Statistical analysis by Student't' test. Confidence intervals mean, minimum and maximum values were calculated for each

decade of age group. Confidence interval high represents 95th percentile value in a given group.

RESULTS

During the study period October 2003 to September 2005, serum total PSA of 117 subjects with out lower urinary tract symptoms and any other major clinical illness between the age group 40 to 69 years were analyzed. The results are shown in table - 4

Table - 4

Age	**40 –49 y (A)**	**50-59y (B)**	**60-69y(C)**
Number	50	56	11
Mean	0.49	0.99	1.27
Standard deviation	0.27	0.58	0,71
Median	0.40	0.77	1.34
Standard error of mean	0.038	0.077	0.22
Lower 95% CI	0.416	0.838	0.85
Upper 95% CI	0.564	1.142	1.69
Min -Max	0.05 –1.10	0.10-2.30	0.41 –2.20
Range	1.05	2.20	1.79
P value	A vs. B = 0.000	B vs. C= 0.190 F=0.170	A vs. C = 0.000

Using the 95th percentile CI, the recommended age-specific reference ranges of total PSA values were as follows: for the age group 40 –49 years 0.564 ng/ml, 50-59years 1.142 ng/ml respectively, and for the age group 60-69years serum PSA 95th percentile value is 1.69 ng/ml. The minimum value of total serum PSA detected was 0.05 ng/ml and the maximum value of serum PSA was 2.30 ng/ml

The mean PSA value increased from 0.49 for men aged between 40 to 49 years to 1.27 for men aged between 60-69 years. The increase was statistically significant (p =0.000).

The mean total PSA value increased from 0.99 for men aged between 50 to59 years to 1.27 were for men aged between 60 to 69 years. But the increase was not statistically significant (P =0.190), this may be because of the small sample size (9.4%) in the age group 60 to 69 years. Serum PSA was detected in the sera of all the 117 subjects.

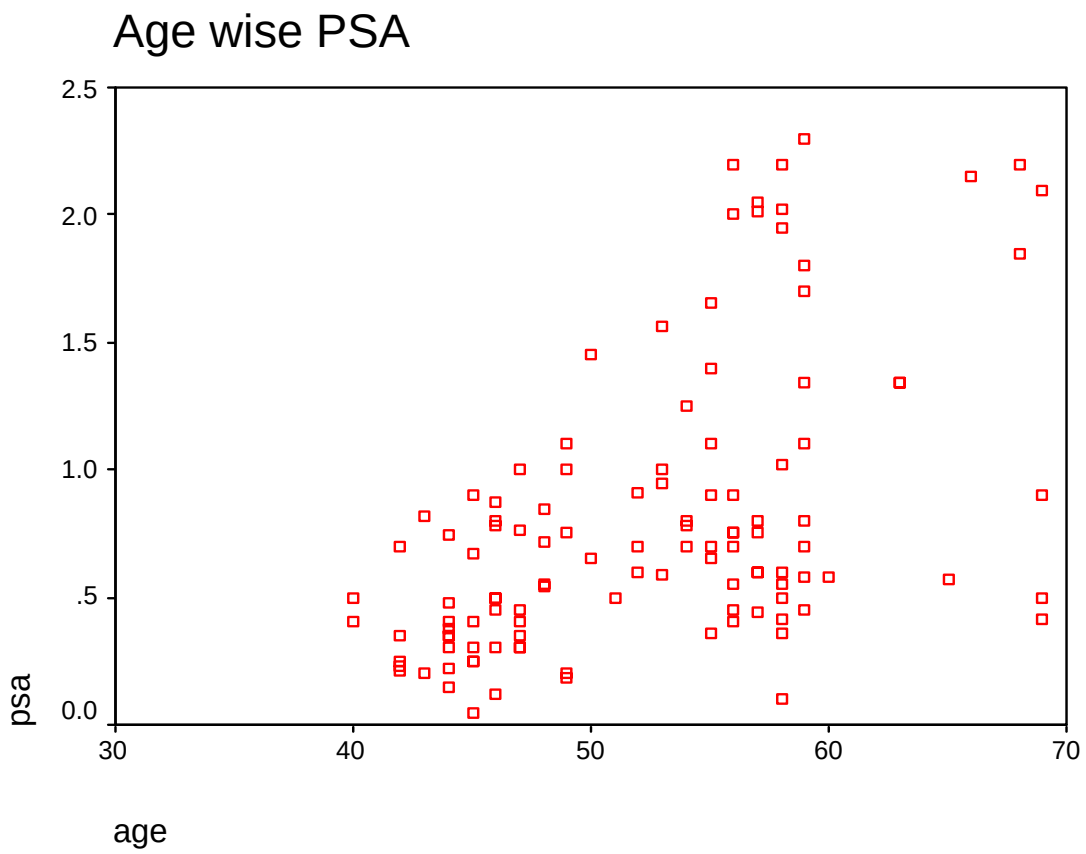
DISCUSSION

Total PSA (tPSA) is a widely used tumour marker for the early detection and monitoring of patients with prostate cancer. While PSA testing has resulted in an increase in prostate cancer detection, its routine use has been questioned because of lack of specificity. Racial variations of PSA values were observed.

Studies have shown that race may also be an important factor in setting a reference range Enormous efforts were made to establish age specific reference ranges through out the world. Black men with prostate cancer have higher PSA levels[33,40] than whites even after adjustment for age and stage of the disease. Morgan et al[33] showed that using standard age specific reference ranges 41 % of cancers were missed in black men and suggested the following reference range for black men; for men in their 40s, 0 to 2ng/ml, for men in their 50s 0 to 5ng/ml, for men in their 60s 0 to 4.5 ng /ml, and 0 to 5.5 ng/ml for men in their 70s.

Extensive work by osterling[32, 35] group on American whites and Japanese men clearly showed age specific significant increase for 95 percentile with advancing age.

Our study also shows age specific significant increase for 95-percentile value (fig 1)



		age	psa
age	Pearson Correlation	1	.526(**)
	Sig. (2-tailed)	.	.000
	N	116	116
psa	Pearson Correlation	.526(**)	1
	Sig. (2-tailed)	.000	.
	N	116	116

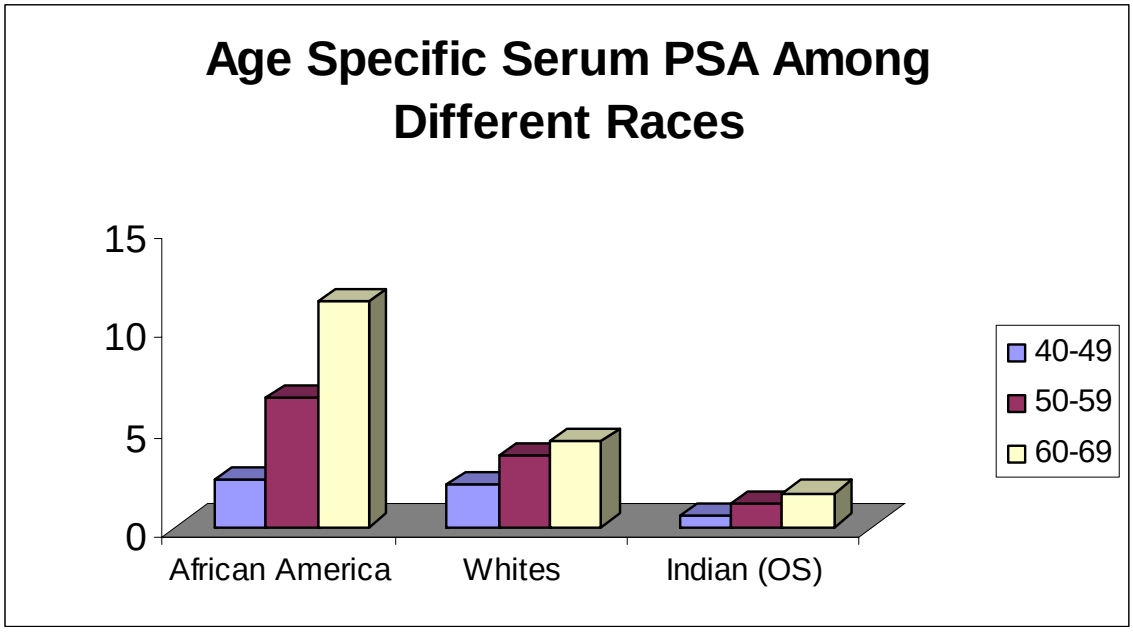
** Correlation is significant at the 0.01 level (2-tailed).

Age specific PSA Figure 1

Myrtel[53] et al found that 100 % of healthy men less than 40 years and 97 % of men over age 40 had a serum PSA below or equal to 4 ng/ml.

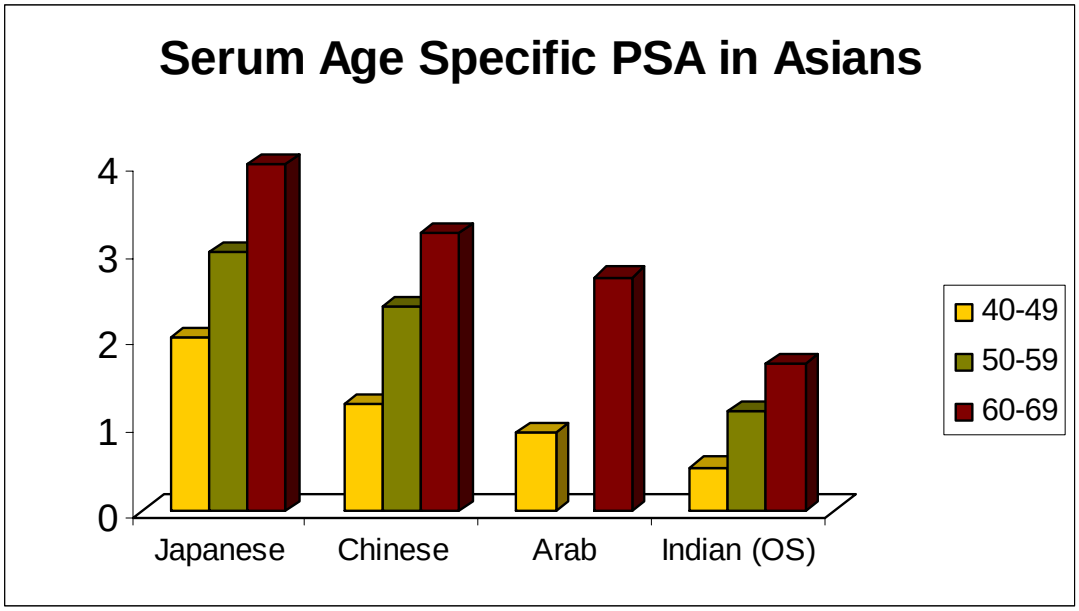
Our study shows a similar finding and in none of our patients between the age group of 40 –69 serum PSA was more than 4 ng/ml.

Studies have shown that age-specific reference ranges for serum PSA were significantly lower for Asians than Western men [15,32,34,41]. Our study also shows a low age specific PSA values compared to Western men. (Fig.2)



(Fig.2)

Study conducted at the department of biochemistry punjagutta[34] India has shown the age specific reference ranges were 1.39 for men aged 40-49, 1.48 for men aged 50 to59, 1.609 for men aged 60 to 69years, 2 for men aged 70 to79 and 2.47 for men aged 80 to 89. Our results were found to be similar to their results.



(Fig.3)

Study conducted at the department of biochemistry punjagutta[34] India has also shown that Indian males have very low serum PSA concentrations compared with men from other Asian countries. Our study also shows low age specific PSA concentrations than men from other Asian countries (Fig.3).

Comparative data's are shown in table - 5

Table – 5

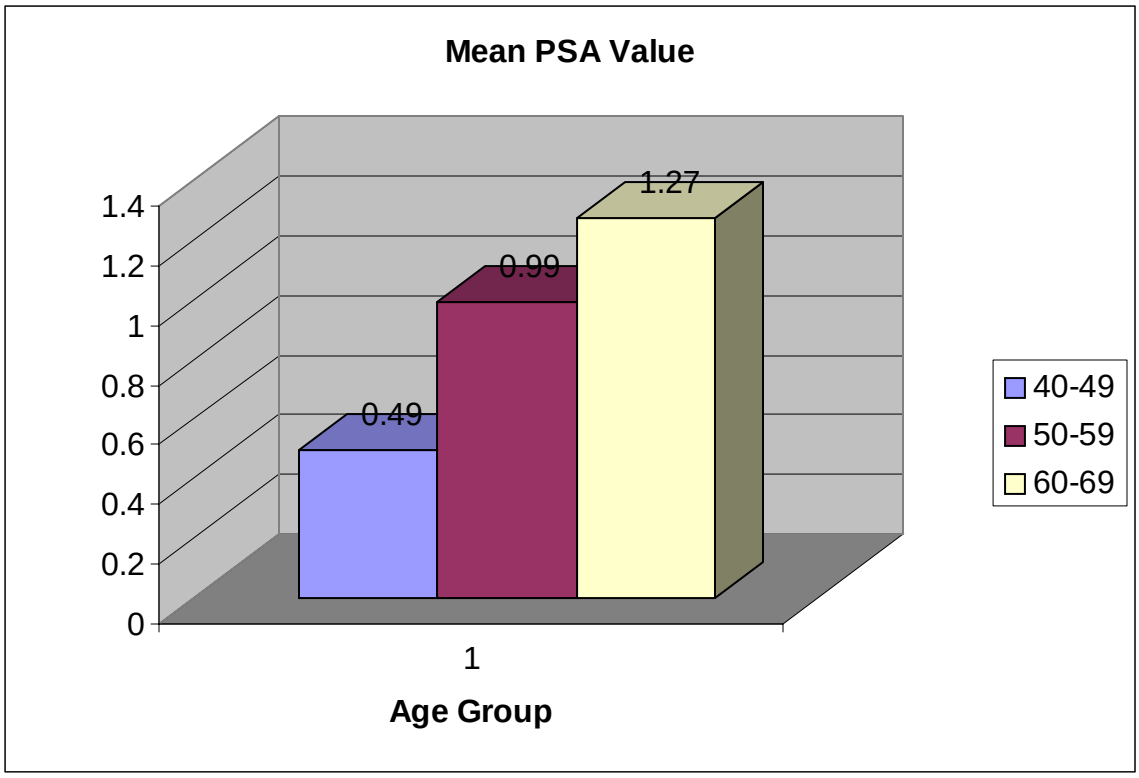
Age specific PSA -95 Percentile value

Author (year, n)	**Population**	**<40 yrs**	**40-49 yrs**	**50-59 yrs**	**60-69 yrs**	**70-79 yrs**	**>80 Yrs**
Morgan et al.[33] 1996 N=b1673 W =1802	Afro Americans US Whites	-	2.4 2.1	6.54 3.6	11.3 4.3	12.5 5.8	-
Dalkin et al[42] 1993,n=728	USA			3.5	5.4	6.3	
Oesterling [35]et al 1993 N =471	Whites	-	2.5	3.5	4.5	6.5	-
Oesterling et al[32] 1995.N=286	Japanese	-	2	3	4	5.0	-
Cooney KA[43]. 2001 N =943	Michigan African-American			2.36			5.59
Wu TT et al[41]-2000 N =1,236	Chinese			4		6	
Wang MZ[15]. 2003 N=1,096	Chinese	1.21	1.23	2.35	3.20	3.39	-
Kehinde EO et al [14] 2005 N=396	Arab		0.9		2.7	5.5	
Our study 2005 N=117	Indian		0.564	1.142	1.69		

Anderson et al[44] found that the published age specific reference ranges were too high for men younger than 60 and too low for men aged 70 –79 years. Their proposed upper limit of normal were 1.5 ng/ml for men 40-49 years, 2.5 ng/ml for 50 to 59 years, 4.5 ng/ml for 60-69 years, and 7.5 ng/ml for men 70-79 years. Even though our study population did not include men in there 70s, our study also shows low age specific reference values for men less than 69 years.

In our study the mean value of serum PSA was 0.49 for 40 – 49 years, 0.99 for 50-59 years and 1.27 for 60-69 years (Fig.4). There was an increase in mean PSA value with increase in age, and the difference was statistically significant.

Kamal BA et al[17] showed similar results in Saudi men. The mean values were 0.87 for men 40-49 years, 1.36 for men 50-59 years, 1.81 for men 60-69 years, 2.32 for men 70-79 years and 2.36 for men 80-89 years.



(Fig.4)

Battikhi MN et al[16] studied age-specific reference ranges of TPSA and FPSA. Recommended values of TPSA and FPSA were, 2.3 and 0.51 ng/ml for 30-34 y; 2.9 and 0.59 ng/ml for 35-39 y; 3.2 and 0.63 ng/ml for 40-44 y; 3.75 and 0.71 ng/ml for 45-49 y; 3.8 and 0.83 ng/ml for 50-54 y; 3.75 and 0.96 ng/ml for 55-59 y; 4.3 and 1.26 ng/ml for >60 y old respectively. Similar to our study (Fig.5) they showed a continuous increase in TPSA. They also showed increase in FPSA with a significant correlation ($P<0.001$, $P<0.05$)

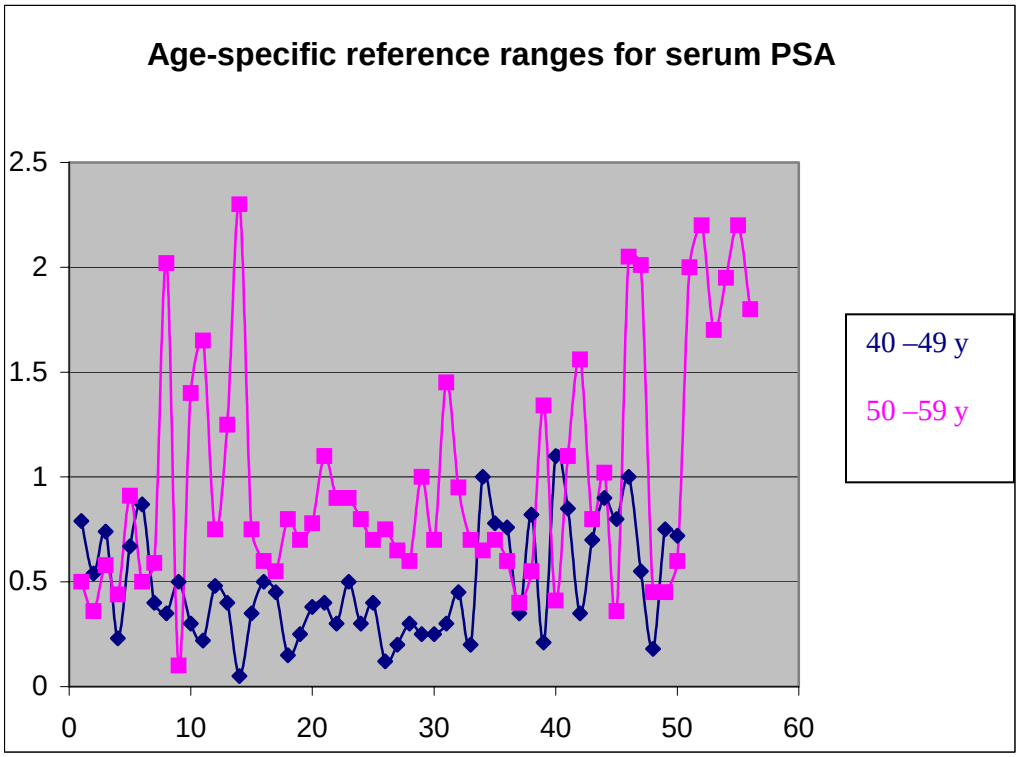


Fig.5

Only two variables are shown in Fig.5. Serum PSA range in the age group 60 – 69 was not shown due to the small size (9%).

El galley et al[36] (largest analysis) supported the use of age specific reference ranges because of demonstrated increase in sensitivity and increase in specificity in older men and subsequent decrease in biopsy in older men.

Catalona WJ et al[13] found that percent free PSA and age-specific PSA cutoffs enhanced PSA specificity for cancer detection, but percent free PSA maintained significantly higher sensitivities. They showed that the %fPSA and PSAD were more sensitive (95% sensitivity) and age-specific PSA cutoffs missed 20% to 60% of cancers in men older than 60 years of age. The prostatic volume (KUBU) in our study ranges from 16 – 28ml.

Ito K et al[12] also found that using the age-specific PSA reference range the sensitivity, specificity, and efficiency increased to 92.4%, 91.2%, and 84.3%, respectively. The diagnostic efficiency of the age-specific PSA reference range was optimal with cutoff values of 3.0, 3.5, 4.0, 4.0, and 7.0 ng/mL in subjects 60 to 64, 65 to 69, 70 to 74, 75 to 79, and older than 80 years of age, respectively. All of the cases of prostate cancer detected were clinically significant.

Studies[32,35,42,44] have clearly shown the importance of age specific reference range and the importance of knowing the race. The clinical meaning of a given PSA varies from one race to the other.

Investigators have recommended age specific prostate specific reference ranges based on ethnicity[3]. (Table-6)

Recommended Age Specific Prostate Specific Reference Ranges[3]. (Controversial)

Table – 6

Age Years	White ng/ml	Specificity %	Black ng/ml	Specificity %	Asian ng/ml	Specificity %
40-49	2.5	95	2.0	93	2.0	95
50-59	3.5	95	4.0	88	3.0	95
60-69	4.5	95	4.5	81	4.0	95
70-79	6.5	95	5.5	78	5.0	95

Osterling et al[45] concluded that by using age specific reference ranges for serum PSA the sensitivity decreased by 9%, the specificity increased by 11% and the over all positive predictive value increased by 5%.

SUMMARY

Aim

To determine age-specific reference ranges for serum prostate-specific antigen (PSA) concentration in South Indian men.

Study design

Cross sectional study.

Setting

This study analyzed the PSA value of 117 subjects with out lower urinary tract symptoms during the period October 2003 to September 2005 at Government General Hospital. Chennai -3

Inclusion criteria

1. Individuals attending Urology clinics for minor illness
2. Normal healthy volunteers.

Exclusion criteria

1. Subjects with history of lower urinary tract symptoms
2. Subjects with history of recent urethral instrumentation.
3. Subjects with history of recent catheterization
4. Patients with history of Prostatitis

Data collection

Our study group consisted of 117subjects belonging to the subpopulation of Chennai from south India of different age groups ranging from 40 to 69 years. Detailed history was taken and a complete clinical examination was done. Blood biochemical analysis and urine analysis was done for all patients. Ultrasound KUBU, digital rectal examination was done in all selected subjects. Complete questionnaire is shown in appendix 1 Serum PSA was estimated[29] using ELISA, and Bayer ADVIA centaur assay kits (last 25 patients).

Case definitions

Subjects referred to urology department for evaluation of renal cyst, back pain, renal microlith, infertility were included in the study. Three cases of renal calculi with out urinary tract infection were also included in the study. Healthy volunteers (hospital workers, patient's attenders) after through examination and history taking were also included in the study group.

Statistical analysis

Statistical analysis by Student ‘t’ test. Confidence intervals mean, minimum and maximum values were calculated for each decade of age group. Confidence interval high represents 95th percentile value in a given group.

Results During the study period October 2003 to September 2005, serum total PSA of 117 subjects with out lower urinary tract symptoms and any other major clinical illness between the age group 40 to 69 years were analyzed.

Using the 95th percentile CI, the recommended age-specific reference ranges of total PSA values were as follows: for the age group 40 – 49 years 0.564 ng/ml, 50-59years 1.142 ng/ml respectively, and for the age group 60-69years serum PSA 95th percentile value is 1.69 ng/ml. The minimum value of total serum PSA detected was 0.05 ng/ml and the maximum value of serum PSA was 2.30 ng/ml.

The mean PSA value increased from 0.49 for men aged between 40to49 years to 1.27 for men aged between 60-69 years. The increase was statistically significant (p =0.000).

The mean total PSA value increased from 0.99 for men aged between 50 to59 years to 1.27 for men aged between 60 to 69 years. But the increase was not statistically significant (P =0.190), this may be because of the small sample size (9.4%) in the age group 60 to 69 years. Serum PSA was detected in the sera of all the 117 subjects

CONCLUSION

1. The serum PSA concentration directly correlates with the patient's age. Thus, rather than relying on a single reference range for men of all age groups, it is more appropriate to have age-specific reference ranges.

2. Age-specific reference ranges have the potential to make serum PSA a more discriminating tumor marker for detecting clinically significant cancers in older men and to find more potentially curable cancers in younger men.

3. Age and race specific reference range will help in developing specific algorithm for different population to detect adenocarcinoma of the prostate at an earlier stage.

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APPENDIX I

PROFORMA

Age-specific reference ranges for serum prostate-specific antigen (PSA) concentration in south Indian men.

Name :

Age :

I.D. No. :

Diabetic	:	Yes	No
Hypertensive	:	Yes	No
Smoker	:	Yes	No
Alcoholic	:	Yes	No
Surgery	:	Yes	No
Medication	:	Yes	No

Inclusion criteria

3. Individuals attending urology clinics for minor illness
4. Normal healthy volunteers

Exclusion criteria

5. Subjects with history of lower urinary tract symptoms
6. Subjects with history of recent urethral instrumentation
7. Subjects with history of recent catheterization

8. Patients with history of Prostatitis

Investigations :

Hb		Blood	Urea
Urine	Albumin		Sugar
	Sugar		Creatinine
	Deposits		

USG KUBU

Serum PSA

Clinical Examination

Per Rectal Examination

Prostate :	Consistency
	Grade

APPENDIX - II
MASTER CHART

S. No.	Name	Age	Diabetic	Hypertensive	Surgery	Medications	S.PSA ng/ml
1.	Thangaraj	44	-	-	-	-	0.79
2.	Muthu	48	-	-	-	-	0.54
3.	Sundar	44	-	-	-	-	0.74
4.	Murugan	42	-	-	-	-	0.23
5.	Elappan	45	-	-	-	-	0.67
6.	Kandasamy	46	-	-	-	-	0.87
7.	Mani	40	-	-	-	-	0.40
8.	Annamalai	44	-	-	-	-	0.35
9.	Sekar	46	-	-	-	-	0.50
10.	Mohammed	47	DM	-	-	Daonil	0.30
11.	Padmanaban	44	-	-	-	-	0.22
12.	Pakirisamy	44	-	-	-	-	0.48
13.	Kumar	47	-	-	-	-	0.40
14.	Ranga Rajan	45	-	-	-	-	0.05
15.	Arjun	42	-	-	-	-	0.35
16.	Chandrasekar	40	-	-	-	-	0.50
17.	Shivalingam	46	-	-	-	-	0.45
18.	Srinivasan	44	-	-	-	-	0.15
19.	Subramani	45	-	-	-	-	0.23
20.	Sivakumar	44	-	-	-	-	0.38
21.	Ahmed Basha	45	-	-	-	-	0.40
22.	Thillai Govindan	47	-	-	-	-	0.30
23.	Seetharam	46	-	-	-	-	0.50
24.	Muniratnam	45	-	-	-	-	0.30
25.	Paneer	45	-	-	-	-	0.40
26.	Balakumar	46	-	-	-	-	0.12
27.	Venkatesh	43	-	-	-	-	0.20
28.	Muthusawmy	44	-	-	-	-	0.30
29.	Chandran	45	-	-	-	-	0.25
30.	Thangaraj	42	-	-	-	-	0.25
31.	Ramakrishnan	46	-	-	-	-	0.30
32.	Jaganathan	46	-	-	-	-	0.45
33.	Ramalingam	49	-	-	-	-	0.20
34.	Shankar	49	-	-	-	-	1
35.	Abdul Kareem	46	-	-	-	-	0.78
36.	Durai Raj	47	-	-	-	-	0.76
37.	Ganesan	47	-	-	-	-	0.35
38.	Mohan Raj	43	-	-	-	-	0.82
39.	Saunder	42	-	-	-	-	0.21
40.	Thangam	49	-	-	-	-	1.10
41.	Thirumurgan	48	-	-	-	-	0.85
42.	Raman	44	-	-	-	-	0.35
43.	Tholkapian	42	-	-	-	-	0.70
44.	Umapathy	45	-	-	-	-	0.90
45.	Baskaran	46	-	-	-	-	0.80
46.	Krishnamoorthy	47	-	-	-	-	1.00
47.	Muthaiah	48	-	-	-	-	0.55
48.	Abdul Razak	49	DM	-	-	Diet Control	0.18

49.	Prabakaran	49	-	-	-	-	0.75
50.	Venkatesan	48	-	-	-	-	0.72

S. No.	Name	Age	Diabetic	Hypertensive	Surgery	Medications	S.PSA ng/ml
51.	Rajendren	58	-	-	-	-	0.50
52.	Kannappan	55	-	-	-	-	0.36
53.	Rangasamy	59	-	-	-	-	0.58
54.	Swamy	57	-	-	-	-	0.40
55.	Esupatham	52	-	-	-	-	0.90
56.	Jayamurthy	51	-	-	-	-	0.50
57.	Vetrivel	53	-	-	-	-	0.59
58.	Thripathy	58	-	-	-	-	2.02
59.	Veerasamy	58	-	-	-	-	0.10
60.	Muthupandian	55	-	-	-	-	1.40
61.	Subramanian	55	-	-	-	-	1.65
62.	Sa Mohammed	56	-	-	-	-	0.75
63.	Ratinavel	54	-	-	-	-	1.25
64.	Subramanian	59	-	HT	-	Atenolol	2.30
65.	Narayanasamy	57	-	-	-	-	0.75
66.	Sivakumar	58	-	-	-	-	0.60
67.	Govindasamy	56	-	-	-	-	0.55
68.	Shakir Ahamed	57	-	-	-	-	0.80
69.	Balaraman	59	-	-	-	-	0.70
70.	Durai Raj	54	-	-	-	-	0.78
71.	Rajagopal	55	-	-	-	-	1.10
72.	Mohammed	55	-	-	-	-	0.90
73.	Ramachadran	56	-	-	-	-	0.90
74.	Khader	54	-	-	-	-	0.80
75.	Govindan	55	-	-	-	-	0.70
76.	Arunachalam	56	-	-	-	-	0.75
77.	Poongavanam	50	-	-	-	-	0.68
78.	Jawahar	52	-	-	-	-	0.60
79.	Subramanian	53	-	-	-	-	1.00
80.	Nandalal	52	-	-	-	-	0.70
81.	Ardhanari	50	-	-	-	-	1.44
82.	Marimuthu	53	-	-	-	-	0.95
83.	Kamal Basha	54	-	-	-	-	0.70
84.	Mathews	55	DM	-	-	Daonil	0.65
85.	Senthamarai	56	-	-	-	-	0.70
86.	Malayandi	57	-	-	-	-	0.60
87.	Natarajan	56	-	-	-	-	0.40
88.	Govinda Rajan	58	-	-	-	-	0.55
89.	Krishna Murthy	59	-	-	-	-	1.34
90.	Mahalingam	58	-	-	-	-	0.41
91.	Amirtham	59	-	-	-	-	1.10
92.	Durai	53	-	-	-	-	1.56
93.	Desai	59	-	-	-	-	0.80
94.	Veeraragavan	58	-	-	-	-	1.02
95.	Subramani	58	-	-	-	-	0.36
96.	Ranganathan	57	-	HT	-	Atenolol	2.05
97.	Mannan	57	-	-	-	-	2.01
98.	Jayabal	59	-	-	-	-	0.45
99.	Thangaraj	56	-	-	-	-	0.45
100.	Balakrishnan	57	-	-	-	-	0.60

S. No.	Name	Age	Diabetic	Hypertensive	Surgery	Medications	S.PSA ng/ml
101.	Jayapal	56	-	-	-	-	2.00
102.	Muthu	56	-	-	-	-	2.20
103.	Chakaravathy	59	-	-	-	-	1.70
104.	Jayavel	58	-	-	-	-	1.95
105.	Mani	58	-	-	-	-	2.20
106.	Razak	59	-	-	-	-	1.80
107.	Rajagopalan	69	-	-	-	-	0.50
108.	Govindan	65	-	-	-	-	0.57
109.	Krishnamurthy	63	-	-	-	-	1.34
110.	Mahalingam	69	-	-	-	-	0.41
111.	Karunakaran	69	DM	-	-	Daonil	0.90
112.	Krishnasamy	68	-	-	-	-	1.85
113.	Ramani	66	-	-	-	-	2.15
114.	Subramani	69	-	-	-	-	2.10
115.	Perumal	68	-	-	-	-	2.20
116.	John Mathews	63	-	-	-	-	1.34
117.	Krishnan	60	-	-	-	-	0.58